Remarks

The Examiner has restricted pending claims 1-109 into Groups 1-35 as set out in the Restriction Requirement. Also, the Examiner indicated that if any of Groups 1-7 were elected, 13 additional species elections were to be made. Applicants have responded to the restriction requirement for completeness of response, but Applicants intend to pursue claims directed to a single-chain protein comprising a heavy chain variable region comprising an amino acid substitution or deletion at position 11. The claims have been amended to reflect this subject matter. The amendment to the claims does not include new matter.

Election

Applicants hereby elect, with traverse, Group II, directed to the binding domain polypeptide of the invention linked to a polypeptide effector, for examination in the application. Claims 1-36, 37 (in part), 38-58, and 61-75 correspond to elected Group II. With respect to the species election, Applicants elect, with traverse, the species as follows:

1. Species A) serine
2. Species B1) CD20
3. Species B2) 2H7
4. Species J3) CD20
5. Species E4) induction of immune effector cells
6. Species G5) secretory pathway components
7. Species C6) B cells
8. Species B7) lymphokines
9. Species A8) bacterium
10. Species A9) anthrax toxin
11. Species B10) tetrodotoxin
12. Species A11) human
13. Species A12) human hinge

Applicants note that pursuant to MPEP §809.02(a), the Examiner is required to examine the generic claim together with the species and that, upon allowance of a generic

claim, Applicants will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim.

Traversal

A. Traversal of Restriction into Groups 1-35

Applicants submit that the restriction of the claims into Groups 1-35 is improper and should be withdrawn.

The Examiner asserts that the inventions of Groups 1-35 are separate and distinct products, which are made by materially different methods, and are used in materially different methods which have different modes of operation, different functions and different effects (Section 4, page 9 of the Restriction Requirement).

A restriction is proper when the application contains independent or distinct inventions (MPEP §803). Independent inventions means that there is no disclosed relationship between the two or more inventions claimed, *i.e.*, they are unconnected in design, operation or effect. Related inventions are distinct if the inventions as claimed are not connected in at least one of design, operation or effect (MPEP §802.01).

The asserted inventions are neither independent nor distinct. Groups 1-35 are all connected in design, operation and effect and are therefore not independent. The subject matter of all the pending claims (*i.e.*, Groups 1-35) is directed to protein products comprising a first polypeptide having a binding domain polypeptide comprising a heavy chain variable region, a second polypeptide comprising a connecting region attached to said first polypeptide; and a third polypeptide comprising an N-terminally truncated immunoglobulin heavy chain. Therefore, all the products exhibit the same, or similar, structural design, and are thereby connected in design. The immunoglobulin-derived constructs that are the subject of the invention all have the same general operation and effect. Moreover, the Examiner has not put forth any evidence to the contrary. The Examiner merely states that the products do not have the same operation or effect without setting out a rationale supporting this conclusion. Even if a rationale were presented, the Examiner has applied an improper standard for restriction. First, the claimed subject matter need not be the same, or identical,

in order to be connected in design, operation or effect (see MPEP §802.01). Second, the claimed subject matters are not distinct if they are unconnected in any one of design, operation or effect. Rather, claimed subject matters are distinct if they are not connected in at least one of design, operation or effect. MPEP §802.01. To show distinctness, claimed subject matters must be shown to be unconnected in design, operation and effect. The Examiner did not address any design connection. Thus, a *prima facie* base for restriction has not been established.

In addition to the above-identified dispositive basis for withdrawing the restriction requirement, Applicants note that the Examiner asserts that the claimed subject matters "represent separate and distinct products, which are made by materially different methods, and are used in materially different methods which have different modes of operation, different functions and different effects." Restriction Requirement, Section 4, page 9. Applicants acknowledge that the Examiner has not asserted that the claims of any two or more of Groups 1-35 are independent. MPEP §806.05(j) provides the standard for determining whether related subject matters are distinct and, thus, appropriate for restriction. Those criteria are (A) whether the claimed subject matters do not overlap in scope (i.e., are mutually exclusive), (B) whether those subject matters are not obvious variants and (C) whether those subject matters are either not capable of use together or have materially different designs, modes of operation , functions or effects. Each of (A), (B) and (C) above must be met to show that related products are distinct. The Examiner has not addressed (A), whether the claimed subject matters overlap in scope. Further, the Examiner has not established, or even asserted, that the claimed subject maters are incapable of use together, and they clearly are capable of use together. Also the Examiner has not addressed the issue of design, as noted above. Thus, the Examiner has failed to satisfy criterion (C) of MPEP §806.05(j). It is therefore beyond question that the Examiner has not applied the relevant standard of MPEP §806.05(j) to the product claims being restricted. The Examiner's focus on different methods for generating the claimed products is misplaced and is not probative on the issues identified in MPEP §806.05(j). Accordingly, for these reasons as well, a *prima facie* basis for restriction has not been established.

A similar analysis reveals that the Examiner's assertion that the claims of Groups 1-7 differ from the claims of Groups 8-35 also fails to establish a *prima facie* basis

for restricting those two larger claim groups. The Examiner has not shown that the claims of Groups 1-7 (amenable to coupling to other molecules) and Groups 8-35 (no limitation to such coupling) are mutually exclusive is scope [MPEP §806.05(j)(A)]. The open-ended claims of Groups 8-35 would not exclude products coupled to other molecules and, thus, the claim scopes cannot be mutually exclusive. The Examiner also has not established that the subject matters of the two claim groups are not obvious variants [MPEP §806.05(j)(B)]. Finally, the Examiner has not, and cannot, establish that the subject matters are incapable of use together and has not shown that the subject matters reflect materially different designs. Accordingly, a *prima facie* basis for restriction has not been established.

For the reasons given above, the asserted inventions of the application are also not distinct under MPEP §806.05(j). Because the inventions are neither independent nor distinct, the restriction requirement should be withdrawn.

Also, Applicants disagree with the Examiner's classifications and submit that a search of all of the claims would not impose a serious burden on the Examiner. All of the Groups are listed either in class 530, subclass 387.3 (Groups 1, 2, 4 and 13-18) or in class 536, subclass 387.3 (groups 3, 5-12 and 19-35). Class 530 is directed to natural resins or derivatives, peptides or proteins, lignins or reaction products thereof, subclass 387.3 is directed to chimeric, mutated, or recombined hybrid antibodies (e.g., bifunctional, bispecific, rodent-human chimeric, single chain, rFv, immunoglobulin fusion protein, etc.). Class 536 is directed to organic compounds and does not have a subclass 387.3; therefore, such classifications cannot support an assertion of a serious search and examination burden. Further, Applicants disagree that a polypeptide product of the invention coupled to a drug (Group I) may be properly classified as a peptide or protein, whereas a polypeptide product of claim 1 coupled to an isotope (Group 5) is classified as an organic compound. Further, Groups 8-12, directed to various polypeptide products of the invention, are searched as organic compounds, while Groups 19-35, drawn to similar polypeptide products, are searched in class 530 as proteins or peptides.

Applicants submit that none of the asserted inventions are organic compounds as defined by the U.S.P.T.O. classification system and that all the inventions fall within the same group of peptide or protein products. As such, because all the claimed products are in

the same class and subclass, searching and examining the claims together would not impose a serious burden on the Examiner.

Further, the products of the invention are all immunoglobulin-derived polypeptides having the related structures and related functions of immunoglobulins. Because searching the claimed products would not impose a serious burden on the Examiner, the restriction requirement should be withdrawn.

B. Traversal of Species Restriction

The Examiner has imposed thirteen different species elections, which the Applicants traverse for the reasons set out below.

In Section 6 of the Restriction Requirement, the Examiner indicates that a particular amino acid at position 11 in the polypeptide construct must be elected (species A-K), contending that substitution of any one of the amino acids renders the function and structure of the protein unpredictable. The Examiner also states that searching all the amino acids creates a burden for the Examiner because each amino acid has reached a separate status in the art.

Applicants submit that they are not claiming the amino acids themselves, and thus any separate status of the amino acids in the art is not relevant to the claimed product. Further, searching the given sequence with any of the amino acids would not place a serious burden on the Examiner. A single search of the peptide sequence of interest in commonly used search databases would recognize all sequences closely related to the sequence being searched such that all sequences having an amino acid substitution in position 11 in the VH region would be identified. More particularly, substituting the approved symbol "Xaa" at position 11 would be expected to identify sequences, regardless of the particular amino acid at position 11, when searching databases using the terminology required by the U.S.P.T.O. See 37 C.F.R. §1.822(b)(2).

In Section 7 of the Restriction Requirement, the Examiner indicates that Applicants must elect a B cell antigen species from the group consisting of CD19, CD20, CD22, CD37, CD40, CD80, and CD86, reasoning that each of the antigens has a separate function and structure, and that each of the antigens has obtained a separate status in the art.

Applicants submit that the requirement for an election of species is improper because Applicants are not claiming any of the above-mentioned B cell antigens. The claimed subject matter is not the B cell antigens themselves, and the separate structural and functional characteristics and separate status in the art of the B cell antigens is thus not dispositive on the propriety of restricting the relevant claims. As such, the requirement for the election of species should be withdrawn.

In Section 8 of the Restriction Requirement, the Examiner indicates that Applicants must elect a species of scFv from the group consisting of HD37, 2H7, G28-1, FC_2-2, UCHL-1, 5B9, L6, 10A8, 2e12, 40.2.36, G19-4, 1D8, and 4.4.220, reasoning that each species of scFv is considered distinct and unrelated because the scFv is produced by a different hybridoma, has a unique amino acid sequence, and has obtained a separate status in the art. Applicants submit that the requirement for an election of species is improper because Applicants are not claiming any of the above-mentioned scFv. The separate structural and functional characteristics and separate status in the art of the scFv is thus not dispositive on the propriety of restricting the relevant claims. As such, the requirement for the election of species should be withdrawn.

In Section 9 of the Restriction Requirement, the Examiner indicates that Applicants must elect a species of target from the group consisting of CD2, CD3, CD4, CD5, CD6, CD8, CD10, CD11b, CD14, CD19, CD20, CD21, CD22, CD23, CD24, CD25, CD28, CD30, CD37, CD40, CD43, CD50 (ICAM3), CD54 (ICAM1), CD56, CD69, CD80, CD86, CD134 (OX40), CD137 (41BB), CD152 (CTLA-4), CD153 (CD30 ligand), CD154 (CD40 ligand), ICOS, L6, B7-H1, and HLA class II, reasoning that each of the targets has a separate function and structure, and that each of the targets has obtained a separate status in the art. Applicants submit that the requirement for an election of species is improper because the subject matter of the claims is not any of the above-mentioned targets. The separate structural and functional characteristics and separate status in the art of the target is thus not dispositive on the propriety of restricting the relevant claims. As such, the requirement for the election of species should be withdrawn.

In Section 10 of the Restriction Requirement, the Examiner indicates that Applicants must elect a species of immunological activity from the group consisting of

antibody dependent cell-mediated cytotoxicity, complement fixation, induction of apoptosis, induction of one or more biologically active signals, induction of one or more immune effector cells, activation of cellular differentiation, cellular activation, release of one or more biologically active molecules, and neutralization of an infectious agent or toxin. The Examiner contends that each activity is functionally independent and distinct and one of skill in the art would readily appreciate that each of the species is associated with different arms of the immune response. Additionally, the Examiner argues that searching the species would place a serious burden on the Examiner since each of the immunological activities has obtained a separate status in the art. Applicants respectfully disagree.

The species of immunological activity listed above are not mutually exclusive, and more likely are intimately involved with each other. A polypeptide recited in the claims likely carries out one or more of the immunological activities such that it would be impossible to limit the function of the molecule to a single immunological activity. A molecule that activates ADCC necessarily induces induction of biological signals, and some degree of cellular activation, while also causing some induction of immune effector cells and potentially causing release of biological molecules. For example, complement fixation results in activation of complement proteins, release of peptide activators, phagocyte recruitment to the area of inflammation, removal of immune complexes, lysis of certain pathogens and cells, to name just a few downstream activities. See *Immunobiology*, 2nd Ed. Ch. 8, p 8:31-50. Janeway and Travers, eds. Garland Publishing, New York. A single search of the molecule would necessarily encompass the activity for which it is known or used. There is no reason to search for a molecule with either CDC or ADCC or cell activation or apoptosis functions when a search of the molecule itself will identify its activities. Regardless of whether the immunological activities themselves "have acquired a separate status in the art," Applicants are not claiming the activity itself, but a molecule with that activity, which is readily available by a single search of the molecules. As such, the searching does not place a serious burden on the examiner and the requirement for election of an immunological activity should be withdrawn.

In Section 11 of the Restriction Requirement, the Examiner indicates that Applicants must elect a species of biologically active signals from the group consisting of protein kinases, protein phosphatases, G-proteins, cyclic nucleotides or other second

messengers, ion channels, and secretory pathway components. The Examiner contends that each molecule involved in these signals is functionally independent and distinct and one of skill in the art would readily appreciate that each of the species is associated with different pathways in mediating cellular signal transduction. Additionally, the Examiner argues that searching the species would place a serious burden on the Examiner since each of the biologically active signals has obtained a separate status in the art. Applicants respectfully disagree.

Each of the biological signals identified above is not mutually exclusive and the signals often work in concert with each other through many different pathways in mediating cell signaling. For example, protein phosphatases and kinases are usually found in the same signaling pathway, as are G proteins and cyclic nucleotides. Moreover, G proteins, kinases, cyclic nucleotides, ion channels and second messengers are all found in the downstream signals associated with chemokine CCL binding to its receptor on a CNS-derived macrophage. See Shideman et al., "CCL5 evokes calcium signals in microglia through a kinase-, phosphoinositide-, and nucleotide-dependent mechanism," J. Neurosci. Res. 2006, 83:1471-84 (abstract submitted). Thus, regardless of whether the biologically active signals themselves "have acquired a separate status in the art," Applicants are not claiming the activity itself, but a molecule that induces one or more of such signals, wherein the signals are not mutually exclusive. As such, the requirement for an election of species should be withdrawn.

In Section 12 of the Restriction Requirement, the Examiner indicates that Applicants must elect a species of immune effector cell from the group consisting of NK cells, monocytes, macrophages, B cells, T cells, mast cells, neutrophils, eosinophils, and basophils. The Examiner contends that each molecule involved in these signals is functionally independent and distinct and one of skill in the art would readily appreciate that each of the species is associated with different arms of the immune response. Additionally, the Examiner asserts that searching the species would place a serious burden on the Examiner since each of the immune effector cells has obtained a separate status in the art. Applicants respectfully disagree.

As noted above, each biological signal or immunological activity in the immune response works in connection with other components, and arms, of the immune response. Similarly, each cell in the immune response is interconnected with many other cell types and may contain many of the same receptors and signaling mechanisms to carry out similar immune functions. A polypeptide product of the invention may bind to multiple immune cell types having a receptor for an Ig molecule, such as a B cell, a monocyte, an NK cell, and others. A polypeptide of the invention may induce more than one effector cell and induction of one cell type is not mutually exclusive of stimulation of another cell type.

Further, even if the immune effector cells themselves "have acquired a separate status in the art," Applicants are not claiming the cell, but a molecule which induces a cell. As such, the searching performed by the Examiner is for the single molecule type and not every cell type, as asserted by the Examiner. Therefore, searching the invention does not place a serious burden on the Examiner and the requirement for election of an immune effector cell should be withdrawn.

In Section 13, page 20 of the Restriction Requirement, the Examiner indicates that Applicants must elect a species of cytokine from the group consisting of monokines, lymphokines, chemokines, growth factors, colony stimulating factors, interferons, and interleukins. The Examiner contends that each molecule is functionally independent and distinct, contending that one of skill in the art would readily appreciate that each of the species is associated with different arms of the immune response and are therefore unrelated. Additionally, the Examiner argues that searching the species would place a serious burden on the Examiner since each of the molecules has obtained a separate status in the art. Applicants respectfully traverse.

The polypeptide of the invention stimulates many biologically active molecules and each of the molecules noted above is produced exclusively from the others. The molecules often work in concert with each other in functioning in the different arms of the immune response. A polypeptide of the invention having an Ig constant region may bind a B cell, monocyte or other immune cell type and induce activity by cytokines (which include lymphokines, monokines, interleukins, interferons and colony stimulating factors), chemokines, and growth factors. A polypeptide of the invention may induce more than one

biologically active molecule from the group identified above and induction of one biological molecule is not mutually exclusive of induction of another type.

Further, even if the biologically active molecules themselves "have acquired a separate status in the art," Applicants are not claiming that biologically active molecule. As such, the searching performed by the Examiner is for the single molecule type that is the subject of the invention and not every biologically active molecule recited above. Therefore, searching the invention does not place a serious burden on the Examiner and the requirement for election of a biologically active molecule should be withdrawn.

In Section 13, page 21, of the Restriction Requirement, the Examiner indicates that Applicant must elect a species of infectious agent from the group consisting of a bacterium, a virus, a parasite, or a fungus. The Examiner contends that each infectious agent is functionally independent and distinct, contending that one of skill in the art would readily appreciate that each of the species is unrelated. Additionally, the Examiner argues that searching the species would place a serious burden on the Examiner since each of the species has obtained a separate status in the art. Applicants respectfully traverse.

As noted above, the polypeptide of the invention induces several non-mutually exclusive immunological activities, including neutralization of an infectious agent. Applicants are not claiming the infectious agent, but the neutralization activity by the polypeptide of the claims and, as such, the separate status in the art of the agents is not probative on the propriety of restricting the claimed subject matters.

Further, a search of the polypeptides of the claims and neutralization of an infectious agent will necessarily encompass all infectious agents. Therefore, such searching does not place a serious burden on the Examiner and the requirement for election of an infectious agent should be withdrawn.

In Section 14 of the Restriction Requirement, the Examiner indicates that Applicants must elect a species of exotoxin from the group consisting of anthrax toxin, cholera toxin, diphtheria toxin, pertussis toxin, *E. coli* heat-labile toxin LT, *E. coli* heat stable toxin ST, shiga toxin, Pseudomonas Exotoxin A, botulinum toxin, tetanus toxin, *Bordetella pertussis* AC toxin, and *Bacillus anthracis* EF. The Examiner contends that each exotoxin is

functionally independent and distinct, contending that the toxins do not share a core structure and, as such, are patentably distinct. Additionally, the Examiner argues that searching the species would place a serious burden on the Examiner since each of the species has obtained a separate status in the art. Applicants respectfully traverse.

While the exotoxins listed above may be patentably distinct based on their chemical structure, Applicantsare not claiming the exotoxins, or even the use of the exotoxins. Applicant submits that the subject matter claimed in the present application is directed toward polypeptides. As such, the separate status in the art of the exotoxins is not probative on the propriety of restricting the pending claims.

Further, a search of the polypeptides of the claims and of the exotoxins will necessarily encompass all exotoxins listed above. Therefore, such searching does not place a serious burden on the Examiner and the requirement for election of an exotoxin should be withdrawn.

In Section 15 of the Restriction Requirement, the Examiner indicates that Applicants must elect a species of endotoxin from the group consisting of saxitoxins, tetrodotoxin, mushroom toxins, aflatoxins, pyrrolizidine alkaloids, phytohemagglutinins, and grayanotoxins. The Examiner contends that each endotoxin is functionally independent and distinct, contending that the toxins do not share a core structure and, as such, are patentably distinct. Additionally, the Examiner argues that searching the species would place a serious burden on the Examiner, since each of the species has obtained a separate status in the art. Applicants respectfully traverse.

While the endotoxins listed above may be patentably distinct based on their chemical structure, Applicants are not claiming the endotoxins, or even the use of the endotoxins. Applicants submit that the subject matter claimed in the present application is directed toward polypeptides. As such, the separate status in the art of the endotoxins is not probative on the propriety of restricting of the pending claims.

Further, a search of the polypeptides of the claims and of the endotoxins will necessarily encompass all endotoxins listed above. Therefore, searching the invention does

not place a serious burden on the Examiner and the requirement for election of an endotoxin should be withdrawn.

In Section 16 of the Restriction Requirement, the Examiner indicates that Applicants must elect a species of binding domain from the group consisting of human, murine, rat, pig, and monkey binding domains. Applicants assert that a single search for the binding domain structure would necessary encompass all of the species set out above, which share a common immunoglobulin structure, and therefore the searching would not place a serious burden on the Examiner.

In Section 17 of the Restriction Requirement, the Examiner indicates that Applicants must elect a species of hinge region from the group consisting of human hinge, human IgG hinge, human IgA hinge, human IgE hinge, camelid hinge, IgG1 llama hinge, nurse shark hinge, and spotted ratfish hinge. The Examiner asserts that each hinge is distinct and has acquired a separate status in the art for the same reasons as set out in Sections 9 and 10 related to antibodies and Ig structures, i.e., that each is functionally independent and distinct and one of skill in the art would readily appreciate that each of the species is associated with different arms of the immune response. Applicants are claming a polypeptide comprising the hinge regions and not the hinge regions themselves. Also, Applicants submit that a single search for an immunoglobulin hinge region in the context of the present claims would necessarily encompass all the hinge regions listed above and would not place a serious burden on the Examiner.

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Conclusion

Applicants submit that the restriction requirement contained in the outstanding Office Action has been overcome and should be withdrawn. In compliance with their legal requirements, Applicants have also elected claim Group II and the various species elections imposed in the Office Action. Applicants further submit that the application is in condition for allowance and request notification of the same.

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Respectfully submitted,

By _____

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